DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR CHLORINE

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Peer reviewers for the second draft of the Toxicological Profile for Chlorine were:

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ATSDR would like to thank these scientists for their review of the document. When the reviewer's suggestions were followed, or when other revisions obviated the need to respond, no further response is provided herein. Revisions that may have obviated the need to respond included sections that were rewritten, moved, or deleted. Some of the editorial and format suggestions could not be followed without changing ATSDR established format. Additionally, several stylistic changes that were purely arbitrary were not incorporated. Other suggestions made by the reviewers that ATSDR decided not to follow are discussed below. In the discussion that follows, "PR" refers to the appropriate page of the assembled peer review document, "P" indicates a page number in the second draft of the profile, and "L" indicates the line number on that page.

The peer reviewers provided citations and/or copies of papers for studies they would like to see added to the toxicological profile. Data from some of these studies have been incorporated into the toxicological profile.

Review comments provided by John R. Balmes, M.D.

PR9, P34, L32-34: The comment refers to the following sentence: Chest x-rays taken hours after the accident showed air in the mediastinal space (space in the middle of the chest separating the two pleurae) which resolved 7–10 days after the accident." Dr. Balmes states that the sentence is confusing and should be deleted. He further notes that pneumomediastinum is not specific to chlorine and likely resulted from severe coughing.

Response: The fact that pneumomediastinum is not specific to chlorine exposure is not a good reason to delete the sentence. Respiratory irritation, cough, shortness of breath, and other respiratory symptoms also are not specific to chlorine. However, a statement was added to the text indicating that the pneumomediastinum likely resulted from severe coughing.

All other comments provided by Dr. Balmes were addressed as suggested.

Review comments provided by Meryl Karol, Ph.D.

PR23, P3, L3: The comment refers to the section: *How can chlorine enter and leave my body?* Dr. Karol suggests adding the following sentence: *Chlorine is also absorbed following skin contact.*

Response: There is no evidence that chlorine is absorbed following skin contact. No change was made.

PR23, P3, L8-19: Dr. Karol states that the boilerplate text that refers to the use of animals for research is judgmental and out of place in the Public Health overview and should be deleted.

Response: The text in question appears in all Toxicological Profiles and is intended to convey to the general public that animals used in experimental research must be treated humanely. No change was made.

PR24, P4: The comment refers to the row in the table describing effects following *Short-term exposure to hypochlorite solution by ingestion*. The text states that: *Drinking small amounts of hypochlorite solution (less than a cup) can produce irritation of the esophagus.* Dr. Karol suggests adding: *typically of chlorine-treated drinking water* after *(less than a cup).*

Response: The statement in question refers to drinking a solution of hypochlorite, as in bleach, not chlorinated water. No change was made.

PR24, P5: The comment refers to the Section: *How can chlorine affect children?* Dr. Karol states that the section should be reworded because, as written, it appears to contradict statements made elsewhere that children are not small adults. Dr. Karol further states that the text should indicate that the effect of chlorine depends on the concentration and route of exposure and on the age of the child.

Response: The previous section indicates that effects of chlorine in the air depend on the concentration and duration of exposure. It is accurate, as the text indicates, that the effects of chlorine in children are

the same than in adults; however, a statement was added indicating that children may be more sensitive than adults. The effects of chlorine gas are restricted to the site of contact, mainly the respiratory tract, and are not route-dependent since there is no other possible route of exposure.

PR24, P5: The comment refers to the information about birth defect in the section: *How can chlorine affect children?* The text states that a study in rats exposed to hypochlorite solution during pregnancy found no evidence of birth defects or other developmental alterations in the baby rats. Dr. Karol suggests adding the concentrations used in the study.

Response: The text refers to a study by Carlton et al. (1986) in which pregnant Long-Evans rats were treated by gavage with up to 3.4 mg Cl/kg/day. For comparison, the MCL for chlorine is 4 mg/L (4 ppm), which is equivalent to a human dose of approximately 0.1 mg Cl/kg/day assuming consumption of 2 L of water per day and 70 kg body weight. Therefore, the rats were exposed to about 34 times the MCL. Text was added indicating that the rats consumed levels of chlorine much higher than people would via drinking water.

PR24, P10, L17: Dr. Karol states that the terms *alveolar capillary congestion*, which is the cause of pulmonary edema following exposure to high chlorine gas, are unclear.

Response: By definition, congestion is accumulation of fluid within the vessels of an organ or part. ATSDR fails to see why this is unclear to Dr. Karol. No changes were made.

PR25, P12, L25: Dr. Karol suggests providing both ppm and mg/L units throughout the text.

Response: The equivalency between ppm in water and mg/L is indicated the first time units appear in a chapter, but both units will not be displayed together throughout the text.

PR25, P15, L29: Dr. Karol asks for the meaning of *co-principal*, that is used to describe the various studies in volunteers that serve as basis for the acute-duration inhalation MRL for chlorine.

Response: Co-principal means that no single study is significantly better or more reliable than the others and they support each other in terms of similar findings occurring at similar exposure levels. Usually, there is one study, the principal study, which identifies the lowest LOAEL, or the highest NOAEL, or both, and that serves as basis for the MRL. Other studies may have found slightly higher LOAELs and are used as supporting studies.

PR26, P16: Dr. Karol states that justification is needed to use the Kutzman (1983) unpublished study to derive an MRL. Dr. Karol further notes that the Kutzman (1983) study is compromised by the use of animals with underlying lung disease.

Response: It is within ATSDR's guidelines to used unpublished studies for MRL derivation providing that the study is submitted for review (as is now the case for Kutzman [1983]) and the results are found to be valid, even if there are limitations. According to Kutzman (1986), the lungs of controls rats showed a mild low-grade chronic murine pneumonia with minimal focal acute alveolitis, which suggested a recent

bacterial infection. Inspection of Table 10 of Kutzman (1986) shows that the incidence of focal, acute/subacute alveolitis graded slight to moderate was 3/23, 5/23, 6/23, and 4/23 in the controls, 0.5, 1.5, and 5 ppm dose groups, respectively. The lesions used as basis for the MRL were loss of cilia in the trachea, which although did not appear to be concentration-related, exhibited a statistically significant trend.

PR26, Figure 3-1: Dr. Karol states that Figure 1 (presumably Figure 3-1) is too complicated for meaningful interpretation and that it must be simplified.

Response: Instructions for the interpretation of the LSE tables and figures are provided in Appendix B, as indicated on page 27, lines 14-15.

PR26, P31, L1: Dr. Karol notes that the statement that the upper portion of the respiratory tract is the target for exposure should be qualified as to the species (and its breathing pattern) and the exposure concentration.

Response: The information available suggests that the upper portion of the respiratory tract is the target for exposure in humans and in animals regardless of species and breathing patterns. All reliable available exposure concentrations are listed in Table 3-1.

PR26, Table 3-2: Dr. Karol states that Table 3-2, which is taken from Ellenhorn and Barceloux (1988), and lists acute effects of chlorine exposure and the approximate levels at which they occur, should be updated with more recent data.

Response: Unfortunately, a more recent edition of this textbook from 1997 does not have such a table. However, the effects of chlorine and the levels at which they occur have not changed.

PR26, P31, L23: The comment refers to the summary of information on threshold levels for odor perception taken from NIOSH (1976). Dr. Karol asks whether there is information more recent than NIOSH (1976).

Response: There are more recent reviews that summarize this topic, but NIOSH (1976) is the most complete. There is no new relevant information on odor perception.

PR27, P40, L26-33: The comment refers to a summary of a study by Kowitz et al. (1967), which describes symptoms of exposure to chlorine in a group of people following a leak from a cylinder containing chlorine. Dr. Karol suggests adding a statement indicating that without knowledge of exposure concentration or duration, the study has minimal value.

Response: The purpose of the section is to summarize effects observed following high-level occupational exposure using a few representative examples. The studies in this section are not intended to be used for quantitative risk assessment; yet, they provide valuable information.

PR27, P40, L28-29: The comment refers to a sentence stating that the Kutzman (1983) study was used as basis for derivation of an intermediate-duration inhalation MRL for chlorine. Dr. Karol states that an explanation is needed for why the unpublished Kutzman (1983) study was selected as the basis for the MRL derivation.

Response: The rationale for using the Kutzman (1983) as basis for MRL derivation is detailed in Section 2.3.

PR27, P67, L4: The comment refers to the beginning of Section 3.2.2.7 regarding cancer by the oral route of exposure. Dr. Karol states that a brief overview is needed of the carcinogenicity of chlorinated organics that form as a result of chlorination of drinking water and that emphasis should be placed on the concentration of chlorine in the water and the frequency and types of cancers noted.

Response: The introduction to this section clearly states that it is beyond the scope of this profile to discuss the carcinogenicity of chlorinated organics. References to reviews are provided for those interested in this issue.

PR27, P70, L10-13: The comment refers to unpublished information on ocular effects in animals that was taken from a secondary source. Dr. Karol states that unpublished information should not be included in the profile without careful scrutiny of the study.

Response: It is acceptable to cite unpublished information when the original source is unavailable and it is made clear that any conclusions reported are those of the secondary source.

PR27, P70, L17-23: The comment refers to Section 3.2.3.3, *Immunological and Lymphoreticular Effects*, by the dermal route of exposure. The text in question states that Osmundsen (1978) reported cases of allergic contact dermatitis attributed to exposure to sodium hypochlorite. Dr. Karol states that the term "allergic contact dermatitis" should be changed to "contact dermatitis" in agreement Osmundsen's description of the lesion. Dr. Karol further notes that this information should be moved to the section on dermal effects.

Response: The title of Osmundsen's paper is: "Contact dermatitis due to sodium hypochlorite," however, on page 178 of the report Osmundsen concludes: "Although the patient is not aware of contact with hypochlorite prior to every attack of dermatitis, it seems reasonable to accept allergy to hypochlorite as the cause of her complaints". In all the cases described in this section, there has been prior sensitization with hypochlorite; therefore, they are described under *Immunological and Lymphoreticular Effects*.

PR28, Figures 3-4 and 3-5: These figures illustrate the existing information regarding the health effects of chlorine. Dr. Karol states that although the figures are clear and contain some good information, they could be modified to include target organ and LOAEL for each organ, and that it would be helpful to somehow designate the quality of the studies.

Response: The figures in question are standard in all toxicological profiles, but ATSDR will consider some of Dr. Karol's suggestions for future profiles. Target organs and LOAELs are presented in the LSE Tables and Figures.

PR29, P92, L26-27: Dr. Karol states that it is inappropriate to derive an MRL from an unpublished study, especially when peer-reviewed, published studies are available.

Response: As previously mentioned, it is not inappropriate to use an unpublished study as principal study for MRL derivation, as long as the study is eventually peer-reviewed, the conclusions are found to be valid, and it establishes the LOAEL and/or the highest NOAEL.

PR29, P96, L31-33: The comment refers to a paragraph that indicates that several cases of allergic contact dermatitis have been reported. Dr. Karol states that clarification is needed as to whether the reports cited concluded "contact dermatitis" or "allergic contact dermatitis."

Response: All of the studies cited in the paragraph (Eun et al. 1984; Habets et al. 1986; Osmundsen 1978; Van Joost et al. 1987) conducted patch testing and concluded that sensitization to hypochlorite was a strong possibility.

PR29, P97, L27-28: The comment refers to a sentence that suggests that it would be a good idea to examine the nasal cavity of subjects exposed to low levels of chlorine for a long time (as in occupational exposure) in light of the findings in monkeys exposed to chlorine for 1 year (Klonne et al. 1987). It seems that Dr. Karol thought that the profile was suggesting conducting a study in monkeys to evaluate nasal changes. Dr. Karol states that: "it does not seem prudent to suggest undertaking a long-term, low-dose inhalation study in monkeys to evaluate what is expected to be minimal nasal changes."

Response: ATSDR is not suggesting conducting a study in monkeys, but it is suggesting that if epidemiological studies in chlorine workers are conducted, it would be a good idea to evaluate the nasal tissue in the workers in light of the findings in monkeys.

PR29, P104, L1-4: Dr. Karol states without further elaboration "The numbers in Table 5-2 should be checked; there seems to be a problem with columns 3 and 4"

Response: The table was reviewed and the numbers are consistent with the TRI database from which they were derived.

PR29, P104, Section 5.3: Dr. Karol states that reference should be made to Table 5-2 that contains information on uses.

Response: Table 5-2 does not contain information on specific uses other than what is mentioned in the footnotes of the table.

PR30, P108, L2-13: Dr. Karol inquires why, from all of the known accidental spills that have occurred involving chlorine, these reports were selected.

Response: In the limited space and time available for this section, these incidents were deemed both current and representative of the typical amounts of chlorine gas that are released in such accidents.

PR30, P114, L20-28: Dr. Karol states that if this text is a direct quote from the NRC monograph, it should contain quotation marks.

Response: This entire section (lines 16-28) is part of the ATSDR boilerplate for toxicological profiles and not a direct quote from the referenced NRC document.

PR30, P116, Section 6.8.1, *Environmental Fate*: Dr. Karol states that it would be helpful to include the half-life of chlorine released into air as a function of altitude and specify the factors that accelerate or retard its decomposition.

Response: As stated in the profile, Cl_2 has a very short atmospheric lifetime in the troposphere (on the order of several minutes). It is not known whether there is a difference in lifetime as a function of altitude. Since direct photolysis is dependent upon the intensity of sunlight it is possible that factors such as time of year, geographic locations, and time of day affect the rate of direct photolysis. Data regarding the rate of dissociation based on time of year have been added to the profile.

All other comments provided by Dr. Karol were addressed as suggested.

Review comments provided by Dennis Shusterman, Ph.D.

PR37, P38-39: Dr. Shusterman states that several studies of chlorine-exposed pulp mill workers are reviewed, but it is not until the last study that the complexity of pulp mill exposures is mentioned. Dr. Shusterman suggests adding a generic discussion of exposures at the beginning of page 38. He further states that more specific information as to the type of pulp mill (kraft, sulfite) would help establish competing exposures.

Response: There are four studies summarized on pages 38-39 and only two involve pulp mill workers (Enarson et al. 1984; Ferris et al. 1967, 1979); the other two involve chlorine plant workers (Hybak 1999; Patil et al. 1970). In one of the pulp mill studies (Ferris et al. 1967, 1979) there were no adverse effects associated with chlorine exposure, so there is no issue with competing exposures. In the summary of the other pulp mill study (Enarson et al. 1984), the potential confounding of other exposures (sulfur dioxide, hydrogen sulfide, and methylmercaptan, in addition to various particulates) is mentioned in the text. No changes were made.

PR37, P44, L16: Dr. Shusterman seems to be asking for the meaning of “no specific airway pathology”, which is used to describe observations made in rabbits exposed to chlorine and allowed to recover 14 or 60 days in study by Barrow and Smith (1975). Dr. Shusterman wonders whether ATSDR meant to distinguish between “airway pathology” and “pulmonary pathology” (the latter also including alveolar pathology).

Response: The terms “no specific airway pathology” were used by Barrow and Smith (1975) without any further explanation. It will be made clear in the text that these terms are from the investigators.

PR38, P70, L7-13: The comment refers to a sentence stating that instillation of 0.1 mL of household bleach directly to the central corneal surface of the eye of rabbits and followed over a 21-day period produced moderate irritation (Griffith et al. 1980). Dr. Shusterman states that the word "irritation" is more often applied to the conjunctiva, whereas "erosion" is applied to the cornea.

Response: Griffith et al. (1980) used the term "irritation" as an effect involving alterations in the cornea, iris, and conjunctiva. Irritation of the eye involved corneal opacity, hyperemia of the iris, and swelling of the conjunctiva.

All other comments provided by Dr. Shusterman were addressed as suggested.